OPP OFFICIAL RECORD HEALTH EFFECTS DIVISION SCIENTIFIC DATA REVIEWS EPA SERIES 361

CASWELL FILE
108102

SRRD/GCSB TRANSMITTAL SHEET FOR PART B's

Pesticide: <u>Pir</u>	imiphos-Methyl	
Transmitted to I Chem. Tox.#: 33. Sponsor: ICI Am		Chemical#/Case#:2535
CRM: Ruby White	rs	Phone#: 557-2557
This action co EXTENSION ().	entains a request for a Label attached: Yes ()/	DATA WAIVER ()/ TIME No (X)
Branch: Toxicole Completed: 3/22	ogy <u>I</u> , Section <u>II</u>	Reviewer: W. B. Greear Concurrence: Jaco Vallage
	Response, by Guidel	ine
MRID 00080726 Discussion: Recommendation	s: <u>Y/1</u> Data Waiver (),	the bibliography. MRID a 75.4% formulation Tox. 64523 was conducted on a ical is 94.2%
Recommendation		on a 75.4% formulation. 00164523 was conducted on ical is 94.2%.

Compliance Code MRID 00126258	Description: Acute Inhalation/rates: Y/1 Data Waiver ()/ Time Extension () , Study # CTL/P/602 MRID # 00126258 was not conducted on the technical. It was conducted on a 75.4% formulation. Tox category not established. Nominal concentration reported. Technical is 94.2%.
Recommendation	:A study conducted on the technical is required for review.
Compliance Code MRID 00164524 Discussion:	Description: Primary Eye Irritation/rabbit es: Y/1 Data Waiver ()/ Time Extension () , Study # CTL/P/1305 MRID # 00164524 was conducted on a 40% formulation. MRID # 00126257 was conducted on a 75.4% formulation. Tox Category II for 75.4% formulation. MRID # 00080729 is not in the bibliography. Technical is 94.2%. :A study conducted on the technical is required for review.
	1-5 Description: Primary dermal irritation/rabbit es: Y/1 Data Waiver ()/ Time Extension (), Study # NA MRID # 00080728 is not in the bibliography. MRID # 00126257 conducted on a 75.4% formulation. Tox. Category IV. MRID # 00164524 was conducted on a 40% formulation. Technical is 94.2%.
Recommendation	:A study conducted on the technical is required for review.

Compliance Code MRID 00129341	-6 Description: <u>Dermal sensitization/quinea pig</u> s: <u>Y/1</u> Data Waiver ()/ Time Extension (), Study # <u>CTL/P/499</u>
Discussion:	DER of MRID # 00129341 has been examined and appears
	to be adequate (Core-Minimum).
Recommendation	:The study MRID # 00129341 is acceptable for review.
Cuidolino #. 91	-7 Description: Acute delayed neurotoxicity/hen
Compliance Code	es: Y/1 Data Waiver () / Time Extension ()
MRID 00080721	
Discussion:	MRID # 00080721 is not in the bibliography and the
DIDCUDDIO	not in the one-liners. Two studies
	(#'s ICI/49/75220 and an unnumbered study dated
•	6/20/80) are present in Tox files. Both studies are
	unacceptable. Results were uninterpretable, but
	suggestive of a positive response.
Recommendation	:A study is not needed because the 90-day
	neurotoxicity study supercedes the acute study.
Guideline #: 8	2-1(a) Description: 90-day feeding/rodent
Compliance Code	
MRID 00080730	
Discussion:	MRID #'s 00080730 and 00080745 are not in the
	bibliography. A 90-day rat study is listed in the
	one-liners. (Core-Minimum). The DER was examined
	but was too brief to determine the adequacy of
•	study. However, the 2-Yr. chronic/oncogenicity
	study supercedes the requirement for this study.
Recommendation	:The study is not needed for review if the chronic
•	study is acceptable.

Guideline #: <u>82</u> Compliance Code MRID 00080742	-1(b) Description: 90-day feeding/nonrodent s: Y/1 Data Waiver ()/ Time Extension (), Study # NA
Discussion:	MRID's 00080742 and 00080743 are not in the bibliography. A 90-day dog study is listed in the one-liners. (Core-Minimum). The DER was examined but found to be too brief to determine the adequacy of the study. However, a 2-Yr. chronic study supercedes the requirement for the study.
	:The study is not needed for review if the chronic study is acceptable.
Guideline #: 82 Compliance Code MRID 00129342 Discussion:	Description: 21-day dermal/rodent/rabbit es: Y/1 Data Waiver ()/ Time Extension (), Study # 2279-38/59 DER of MRID # 00129342 has been examined and appears to be adequate (Core-Minimum).
Recommendation	:The study MRID # 00129342 is acceptable for review.
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Compliance Code	
DISCUSSION.	The study is not required under current use patterns. Code 7 indicates "criteria not met".
Recommendation	:A study is not needed.

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Compliance Code	2-4 Description: 90-day inhalation/rodent es: N/7 Data Waiver ()/ Time Extension ()
MRID <u>NA</u> Discussion:	
Recommendation	:A study is not needed.
Compliance Code MRID 00126254	
Discussion:	DER of MRID # 00126254 has been examined and appears to be acceptable (Core-Guideline).
Recommendation	:The study MRID # 00126254 is acceptable for review.
Compliance Cod	<u>2-5(b)</u> Description: <u>90-day neurotoxicity/</u> <u>mammalian</u> es: <u>N/7</u> Data Waiver ()/ Time Extension ()
MRID <u>NA</u> Discussion:	, Study # NA
Recommendation	:The study is not needed at this time.
Guideline #: 8 Compliance Cod MRID 00081912	
Discussion:	MRID # 00081912 was not in the bibliography. However, a 2-Yr. Chronic/Oncogenicity study is listed in the one liners. The DER has been examined (study # HO/IH/P/113; 6/74), but was too brief
Recommendation	to determine the adequacy of the study. (Core-Minimum) :The study should be submitted for review after being reformatted.
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Guideline #: 83 Compliance Code MRID 00080749 Discussion:	
Recommendation	:The study should be submitted for review after being reformatted.
Guideline #: 83 Compliance Code MRID 00081912 Discussion:	
Recommendation	:The study should be submitted for review after being reformatted.
Guideline #: 8: Compliance Code MRID 00080746 Discussion:	es: Y/1 Data Waiver ()/ Time Extension ()
Recommendation	:The study should be submitted for review after being reformatted.

Compliance Code MRID 00151623	
Recommendation	:The study MRID # 00151623 is acceptable for review.
Guideline #: 8 Compliance Code MRID 00080734	es: <u>Y/1</u> Data Waiver ()/ Time Extension ()
Discussion:	MRID # 00080734 is not in the bibliography. However, a rabbit study is listed in the one-liners (study # HO/CTL/P/119B). (Core-Minimum) DER of the study has been examined, but is too brief to determine the adequacy of the study.
Recommendation:	The study MRID # 00080734 should be reformatted and submitted for review.
Guideline #: 83 Compliance Code MRID NA Discussion:	NA NA
Recommendation	: <u>NA</u>

	Description: 3-generation reprod./rat es: Y/1 Data Waiver ()/ Time Extension (), Study # 5457/72/853 MRID #'s 00080735 and 00080736 are not in the bibliography. One study # ICI 63/76534, 8/31/76 is listed in the one-liners and is Core-Minimum. A second study # 5457/72/853) is in a Tox memo 2/21/80 and is Core-Minimum. The DER's have been examined but contain too little detail to determine if the studies are adequate.
Recommendation	:The two studies MRID #'s 00080735 and 00080736 should be submitted for review after being reformatted.
Guideline #: 84 Compliance Code MRID 00144969 Discussion:	A-2(a) Description: Gene mutation/Ames es: Y/1 Data Waiver ()/ Time Extension (), Study # (TL/P/962 DER of MRID # 00144969 has been examined and appears to be acceptable. (Acceptable)
Recommendation	:The study MRID # 00144969 is acceptable for review.
Guideline #: 84 Compliance Code MRID 00126256 Discussion:	4-2(b) Description: Struct. chrom. aberration es: Y/1 Data Waiver ()/ Time Extension () _, Study # NA MRID's 00126256 and 00080733 are not in the bibliography. A cytogenetic study in rats (study # 412212, 5/80) is in the one-liners. (No Core- Grade.) DER was examined but was too brief to determine the adequacy of the study.
Recommendation	:The studies should be submitted for review after being reformatted.

Guideline #: <u>84-2(c)</u> Description: <u>Other genotoxic effects</u> Compliance Codes: <u>Y/4</u> Data Waiver ()/ Time Extension () MRID <u>NA</u> , Study # <u>NA</u>		
Discussion:	A new study will be submitted. This is a data gap.	
Recommendation	:The new study will be acceptable for review.	
	-1 Description: General metabolism/rat	
	es: Y/1 Data Waiver ()/ Time Extension ()	
MRID 00129345 Discussion:	, Study # <u>ICI 299/79565</u> MRID #'s 00080738 and 00080737 are not in the	
Discussion:	bibliography. DER of MRID # 00129345 has been	
	examined and appears to be a low-dose repeated-dose	
	study. The single low-and high-dose sections of the	
	metabolism study have not been conducted.	
	(Core-Minimum.)	
Recommendation	:The studies need to be submitted for review after reformatting.	
•		
Guideline #: 85 Compliance Code MRID NA Discussion:	Description: Dermal penetration S: N/7 Data Waiver ()/ Time Extension () , Study # NA Code 7 indicates "Criteria not met". However, It was once proposed to use the chemical to control fleas on carpets. Tox decided, after receiving an exposure assessment, that a dermal penetration study is necessary.	
Recommendation	:The study will be needed if the once proposed use for carpet treatment to control fleas is pursued.	
Guideline #: 80	6-1 Description: <u>Domestic animal safety</u> es: <u>N/NA</u> Data Waiver ()/ Time Extension ()	

MRID NA	, Study # <u>NA</u>
Discussion:	The sponsor failed to indicate a response. However,
	it was once proposed to use the chemical to control
	fleas on carpets. Domestic animals would probably
	receive a significant exposure.
Recommendation	:The study will be needed on the end-use product if
	the once proposed use for carpet treatment control
	fleas is pursued.
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DRAFT Subdivision F Guideline Ref. No. 81-1 Page 2 of November 7, 1989

\$1-1 Acute Oral Toxicity in the Rat

ACCEPTANCE CRITERIA

Individual observations for the entire day of dosing. Observation period to last at least 14 days, or until all test animals appear normal whicheve is longer. Individual daily observations.	1. <u>110</u> 2.•	Technical form of the active ingredient tested. (for reregistration only)
Doses tested, sufficient to determine a toxicity category or a limit dose (5000 mg/kg). Individual observations for the entire day of dosing. Observation period to last at least 14 days, or until all test animals appear normal whicheve is longer. Individual daily observations.	3	Dosing, single orai.
7. Observation period to last at least 14 days, or until all test animals appear normal whicheve is longer. 8. Individual daily observations. 9.* Individual body weights	5	Doses tested, sufficient to determine a toxicity category or a limit dose (5000 mg/kg).
8 Individual daily observations:	7	Observation period to last at least 14 days, or until all test animals appear normal whichever
1. Individual body weights. O • 10 Gross necropsy on all animals and selected animals.	8.	Individual daily observations:
or or one proceed on the comment.	0.• <u> \(\(\) \(\) \(\) \(\)</u>	Gross necropsy on all animals. Silected animals
	Shede	of can be substituted for one conducted with

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DRAFT Subdivision F Guideline Ref. No. 81-2 Page 4 of November 7, 1989

81-2 Acute Dermal Toxicity in the Rat, Rabbit or Guinea Pig

ACCEPTANCE CRITERIA

1. <u>· ^ · / · </u>	Technical form of the active ingredient tested. (for reregistration only)
2.	At least 5 animals/sex/group
3.*	Rats 200-300 gm, rabbits 2.0-3.0 kg or guinea pigs 350-450 gm.
4	Dosing, single dermal.
5.	Dosing, single dermal. Dosing duration at least 24 hours.
6.4.10	Vehicle control, only if toxicity of vehicle is unknown.
7.	Doses tested, sufficient to determine a toxicity category or a finit dose (2000 mg/kg).
8 7	Vehicle control, only if toxicity of vehicle is unknown. Doses tested, sufficient to determine a socicity category or a finit dose (2000 mg/kg). Application site clipped or shaved at least 24 hours before dosing to 32 hours. Application site at least 10% of body surface area.
9. 2	Application site at least 10% of body surface area.
10.	Application site covered with a porous nonirritating cover to retain test material and to
_	
11	individual observations for the entire day of dosing.
12 🗾	
12	
/	is longer.
13.	Individual daily observations.
14.	Individual daily observations. Individual body weights. Gross necropsy on all animals.
15.*	Gross necropsy on all animals.
	Waiver requested but can not be granted based on
	water in person
(ormation provided by the sponsor.
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DRAFT Subdivision F Guideline Ref. No. 81-3 Page 6 of November 7, 1989

81-3 Acute Inhalation Toxicity in the Rat

ACCEPTANCE CRITERIA

1	Technical form of the active ingredient tested. (for reregistration only)
2 🔀	Technical form of the active ingredient tested. (for reregistration only) Product is a gas, a solid which may produce a significant vapor hazard based on toxicity and expected use or contains particles of inhalable size for man (aerodynamic diameter 15 um or
4	less).
3.	At least 5 young adult rate/sex/group
4. <u>~</u>	Dosing, at least 4 hours by inhalation.
5.• <u>~</u>	Chamber air flow dynamic, at least 10 air changes/hour, at least 19% oxygen content.
6. <u>(\) ()</u>	At least 5 young adult rats/sex/group Dosing, at least 4 hours by inhalation. Chamber air flow dynamic, at least 10 air changes/hour, at least 19% oxygen content. Chamber temperature, 22° C (+2°), relative humidity 40-60%. RH ranged from 2.5 - 40°)
7	Monitor rate of air flow
8	Monitor actual concentrations of test material in breathing zone.
9. 👱	Monitor aerodynamic particle size for aerosols. Doses tested, sufficient to determine a toxicity catagory or a limit dose (5 mg/L actual
10. <u>– </u>	Doses tested, sufficient to determine a toxicity catagory or a limit dose (5 mg/L actual
	concentration of respirable substance).
11.	Individual observations for the entire day of dosing.
12.	Observation period to last at least 14 days, or until all test animals appear normal whichever
	is longer.
13.	Individual daily observations.
14.•	is longer. Individual daily observations. Individual body weights.
15.	Gross necropsy on all animals.

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DRAFT Subdivision F Guideline Ref. No. 81-4 Page 8 of November 7, 1989

81-4 Primary Eye Irritation in the Rabbit

ACCEPTANCE CRITERIA

1. <u>//u</u> 2	Technical form of the active ingredient tested. (for reregistration only) $\rightarrow H_{2}^{-1}$ H_{2}^{-1} H_{2}
	2 or ≥ 11.5.
3.*	6 adult rabbits
4. <u> </u>	Dosing, instillation into the conjunctival sac of one eye per animal.
5.*	Dosing, instillation into the conjunctival sac of one eye per animal. Dose, 0.1 ml if a liquid; 0.1 ml or not more than 100 mg if a solid, paste or particulate
	substance.
6. <u>- </u> -	substance. Solid or granular test material ground to a fine dust. (material absence) Eves not washed for at least 24 hours.
7.	Eyes not washed for at least 24 hours.
7 8	Eyes examined and graded for irritation before dosing and at 1, 24, 48 and 72 hr, then daily
	maniferance and manufer of the days (which man is also man)
a	Individual observations for the entire day of dosing. Individual daily observations.
<u>,,, – – </u>	Individual daily observations
10	motivation delig constructions.
	Need straig w/TGAI. Reasons given to support
	Need showy w/ 1011 I
•	every do not apply to 10 eye writation study.
was	ween do not apply to the
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DRAFT Subdivision F Guideline Ref. No. 81-5 Page 10 of November 7, 1989

\$1-5 Primary Dermal Irritation Study ACCEPTANCE CRITERIA

1. <u>no</u> 2. <u>人</u>	Technical form of the active ingredient tested. (for reregistration only) $\frac{1}{2}$
3.	6 adult animals.
4 =	Dosing, single dermal.
5	Dosing duration 4 hours.
6. 🔽	Application site shaved or clipped at least 24 hour prior to dosing.
7. ×	Application site shaved or clipped at least 24 hour prior to dosing. Application site approximately 6 cm ² .
8 ×	Application site covered with a gauze patch held in place with nonirritating tape
8. × 9. ×	Material removed, washed with water, without trauma to application site
10. <u>7/3</u>	Application site examined and graded for irritation at 1, 24, 48 and 72 hr, then daily until
11. × 12. ×	normal or 14 days (whichever is shorter). (1, 22, 49 and 67 hours) Individual observations for the entire day of dosing.
	individual observations for the entire day of dosing.
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	Sponsor will need shely with TGAI
	Energy with 16AL
	alimin o co

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DRAFT Subdivision F Guideline Ref. No. 81-6 Page 12 of November 7, 1989

81-6 Dermal Sensitization in the Guinea Pig

ACCEPTANCE CRITERIA

1. <u>->-</u> 2. ->-	Technical form of the active ingredient tested. (for reregistration only) Study not required if material is corrosive or has a pH of ≤ 2 or ≥ 11.5 . One of the following methods is utilized:	the state of the state of
3.	One of the following methods is utilized;	
 -	Freund's complete adjuvant test	
	Guinea pig maximization test	,
	Split adjuvant technique	
	Buehler test	🛊 में स्टब्स
•	Open epicutaneous test	•
	Maur optimization test	
	Footpad technique in guinea pig	
. /	Other test accepted by OECD (specify)	
	Complete description of test	
6	Reference for test. Test followed essentially as described in reference document.	
7. <u>100</u>	Positive control included. positive control not used in this	study
infi	Positive control included. positive control not used in this formation exists on eseparate study in which positive	Contro-C
was	used north the Buckley procedure.	

DRAFT Subdivision F Guideline Ref. No. 81-7 Page 14 of November 7, 1989

\$1-7 Acute Neurotoxicity in the Hea

ACCEPTANCE CRITERIA

1	Study performed on an organophosphate cholinesterase inhibiting compound.
	Technical form of the active ingredient tested.
3.*	Positive control utilized.
4	Species utilized, domestic laying hen 8-14 months of age.
5	Dosing oral by gavage or capsule (dermal or inhalation may be used).
6	An acute oral LD, is determined.
2 3.* 4. 5. 6. 7. 8.* 10. 11.* 13. 14.	Dose tested equal to an acute oral LD ₃₀ or a limit test of 5000 mg/kg.
8	Dosed animals may be protected with atropine and/or 2-PAM.
	Sufficient test animals so that at least 6 survive.
10	Negative (vehicle) control group of at least 6 hens
11.	Positive control of at least 4 hens. (if used)
	Test dose repeated if no signs of delayed neurotoxicity observed by 21 days after dosing.
13	Observation period 21 days after each dose.
4	Individual daily observations.
15	Individual body weights.
16.	Individual necropsy not required.
17	Histopathology performed on all animals. Tissue to be fixed in situ using whole animal
	perfusion techniques. At least three sections of each of the following tissues:
	brain, including medulla oblongata
	spinal cord; upper cervical, mid-thoracic and lumbro-sacral regions
	tibial nerve; proximal regions and branches
	egistic seame

DRAFT
Subdivision O
Guideline Ref. No. 82-1
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November 8, 1989

82-1 Subchronic Feeding in the Rodent and Nonrodent

ACCEPTANCE CRITERIA

DOES YOU	stary meet the sourcest acceptance	4144 #1:				
1.	Technical form of the active ingredie	ent tested.				
2	At least 10 rodents or 4 nonrodents/sex/group (3 test groups and control group).					
3.	Dosing duration daily for 90-days or					
4.	Doses tested include signs of toxicity at high dose but no lethality in nonrodents or a limit					
-	dose if nontoxic (1000 mg/kg).	·				
5	Doses tested include a NOEL.					
<u>د•</u>	Analysis for test material stability, he	omogeneity and concentration in dosing medium				
7.	Individual daily observations.					
&	Individual body weights.	•				
9.	Individual or cage food consumption					
10.*	Opthalmoscopic examination (at leas	st pretest and at term) control and high dose.				
11	Clinical pathology data of 12 & 13 a	it termination for rodents, before, monthly or midway				
	and at termination for nonrodents.					
12	Hematology.					
	Erythrocyte count	Leucocyte count				
	Hemoglobin	* Differential count				
	Hematocrit	Platelet count (or clotting measure)				
13	Clinical chemistry.					
	Alkaline phosphatase	Total Protein				
	Aspartate aminotransferase	Albumin				
	* Creatinine kinase	Urea				
	Lactic dehydrogenase	Inorganic phosphate				
	Glucose	Calcium				
	Bilirubin	• Potassium				
	Cholesterol	Sodium				
•	· Creatinine	• Chloride				
4.*	•	expected or observed activity. As scheduled in 11.				
	Blood	Total bilirubin				
	Proteia	• Urobilirubin				
	Ketone bodies	Sediment				
•	Appearance	Specific gravity (osmolality)				
	Glucose	*Volume				
5	Individual necropsy of all animals.					
.6		ues performed on all nonrodents and rodents, all control				
		that died or were killed on study, all gross lesions on all				
	animals, target organs on all animal	s and lungs, liver and kidneys on all other animals.				

DRAFT Subdivision O Guideline Ref. No. 82-1 Page 17 of November 8, 1989

aorta	jejunum	peripheral nerve
cycs	bone marrow	kidneys†
	ivert	 , ,
caecum		esophagus
colon	lung†	overies†
duodenum	hymph nodes	oviduct
brain†	stomach	pancreas
skin	mammary gland	rectum
heart†	spleen†	spinal cord (3x)
tested	musculature	thyroid / parathyroids
pituitary	epididymis	salivary glands
ileum	adrenals†	thymus
trachea	uterus	urinary bladder

DRAFT Subdivision F Guideline Ref. No. 82-2 Page 19 of November 7, 1989

82-2 Repeated Dose Dermal Toxicity (21-day) in the Rat, Rabbit or Guinea Pig

ACCEPTANCE CRITERIA

Does you	r study meet the following acceptance	criteria?:					
1	Technical form of the active ingredi	ent tested.					
2							
3.							
4	Application site at least 10% of body surface area.						
	Doses tested include signs of toxicity at high dose, no or minimal dermal irritation, minimal lethality or a limit dose (1000mg/kg) if nontoxic.						
	Doses tested include a NOEL						
	individual daily observations.						
8. <u>~</u>	Individual body weights.						
9	Individual or cage food consumption	L					
10. 120	Cittical battletoff and of 11 er 15	at termination.					
11.	Hematology.						
•	Erythrocyte count	Leucocyte count					
	Hemoglobin	Differential count					
	Hematocrit	Platelet count (or clotting measure)					
12	Clinical chemistry.						
	Alkaline phosphatase	Total Protein					
	Aspartate aminotransferase	Albumin					
	• Vo Crestinine kinase	Urea					
	Lactic dehydrogenase	no inorganic phosphate					
	Glucose	Calcium					
	Bilirubia	Potassium					
	Cholesterol	Sodium					
	• ho Creatinine	* Chloride					
13.• / 10		expected or observed activity. As scheduled in 10.					
	Blood	Total bilirubin					
	Protein	• Urobilirubin					
	Ketone bodies	Sediment					
	Appearance	Specific gravity (osmolality)					
	Glucose	• Volume					
14.	Individual necropsy of all animals.						
15. 🔽		ntrol and high dose animals, all animals that died or were					
	killed on study consisting of all gro	is lesions on all animals, target organs on all animals (to					
		nal and treated) lungs, liver and kidness.					

DRAFT Subdivision F Guideline Ref. No. 82-3 Page 21 of November 7, 1989

82-3 Repeated Dose Dermal Toxicity (90-day) in the Rat, Rabbit or Guinea Pig

ACCEPTANCE CRITERIA

Does you	r study meet the following acceptance	e criteria?:
1	Technical form of the active ingred	ient tested.
2	At least 10 animals/sex/group (3 to	est groups and control group).
3	Dosing duration at least 6 hour/day	daily for 90 days or 5 days/week for 13 weeks.
4	Application site at least 10% of bo	dy surface area.
5	Doses tested include signs of toxici	ty at high dose, no or minimal dermal irritation, minimal 🕟
	lethality or a limit dose (1000mg/k	g) if nontoxic
6.*	Doses tested include a NOEL.	• • • •
7	individual daily observations.	
8	Individual body weights.	
9	Individual or cage food consumption	en. ast pretest and at term) control and high dose.
10.*	Opthalmoscopic examination (at le	ast pretest and at term) control and high dose.
11	Clinical pathology data of 12 & 13	in all animals at termination.
12	Hematology.	
	Erythrocyte count	Leucocyte count
	Hemoglobin	• Differential count
	Hematocrit	Platelet count (or clotting measure)
13	Clinical chemistry.	
	Alkaline phosphatase	Total Protein
	Aspartate aminotransferase	Albumin
	· Creatinine kinese	Urea
	Lactic dehydrogenase	Inorganic phosphate
	Glucose	Calcium
	Bilirubin	Potassium
	Cholesterol	Sodium
	Creatinine	Caloride
14.*		expected or observed activity. As scheduled in 11.
•	Blood	Total bilirubin
	Protein	• Urobilirubin
	Ketone bodies	Sediment
	Арреагансе	Specific gravity (cemolality)
	Glucose	• Volume
15	individual necropsy of all animals.	
16.		sues performed on all nonrodents and rodents, all control
10		that died or were killed on study, all gross lesions on all
•		als and lungs, liver and kidneys on all other animals.
	sorta jejunu	 :
	eyes bone :	narrow kidneys‡

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свесит	liver†	esophagus
colon	lung†	ovaries†
duodenum	lymph nodes	oviduct
brain†	stomach	pancreas
skin	mammary gland	rectum
heart	spicen†	spinal cord (3x)
tata †	musculature	thyroid / parathyroids
pituitary	epididymis	salivary glands
ileum	adrenals†	thymus
trachea	uterus	urinary bladder
t organs to be wei	shed	

DRAFT Subdivision F Guideline Ref. No. 82-4 Page 24 of November 7, 1989

82-4 Subchronic Inhalation Toxicity (90-day) in the Rat

ACCEPTANCE CRITERIA

DOE YOU	n send meer me noncount accedence of	nung:
1	Technical form of the active ingredien	nt tested. (for reregistration only)
2	Product is a gas, a solid which may p	roduce a significant vapor hazard based on toxicity and
	expected use or contains particles of	inhalable size for man (aerodynamic diameter 15 um or
	less).	• •
3	At least 10 young adult rats/sex/group	
4		
5	Food and water should be withheld d	
		air changes/hour, at least 19% oxygen content.
<u>7. —</u>	Chamber temperature, 22° C (±2°), r	
8	Alternatively, oro-nasal or head only	exposures may be used.
9	Monitor rate of air flow,	
10	Monitor actual concentrations of test	
11. —	Monitor aerodynamic particle size for	erosois.
12 —	Individual daily observations.	
13	Individual body weights.	·
14	Individual or cage food consumption.	
15.*		pretest and at term) control and high dose.
16		all animals at termination.
17	Hematology.	I avenue anno
	Erythrocyte count	Leucocyte count Differential count
	Hemoglobia Hematocrit	
18.	Clinical chemistry.	Platelet count (or clotting measure)
	•	Total Protein
	Alkaline phosphatase Aspartate aminotransferase	Albumin
	* Creatinine kinase	Urea
	Lactic dehydrogenase	Inorganic phosphate
	Glucose	Calcium
	Bilirubin	Potassium
	Cholesterol	Sodium
è	Creatinine	• Caloride
19 •		pected or observed activity. As scheduled in 16.
··· —	Blood	Total bilirubin
	Protein	• Urobilirubia
	Ketone bodies	Sediment
	Appearance	Specific gravity (osmolality)
	Glucre	• Volume

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21	and high dose anima	als, all animals that died	med on all nonrodents and rodents, all or were killed on study, all gross lesion gs, liver and kidneys on all other anim	ns on all
	aorta	ieiunum	peripheral nerve	
	EVES .	bone marrow	kidneys†	
	caecum	liver†	esophagus	
	∞lon	· lung†	ovaries†	
	duodenum	lymph nodes	oviduct	
	brain†	stomach	pancreas	
	skin	mammary gland	rectum	
	heart†	spleen†	spinal cord (3x)	
	testes†	musculature	thyroid / parathyroids	
	pituitary	epididymis	salivary glands	· 1 w
	ileum	adrenals†	thymus	
	trachea	uterus	urinary bladder	

grioge completion

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82-5 Subchronic Neurotoxicity (90-day) in the Hen

ACCEPTANCE CRITERIA

·	Study performed ou an organophosphiate chomicaterase minoriting compound.	
2.	Technical form of the active ingredient tested.	
	Positive control utilized. (recommended but optional)	
	Species utilized, domestic laying hen 8-14 months of age.	
	At least 10 animals/sex/group [3 test groups, a positive control (optional) and a negation	ive
	(vehicle) control group].	, d ees-
6	Dosing duration at least daily for 90 days or 5 days/week for 13 weeks.	•
7	Dose route oral gavage or capsule. (dermal or inhalation may be appropriate) Doses tested include signs of toxicity at high dose, no or minimal lethality	
8. 🔀	Doses tested include signs of toxicity at high dose, no or minimal lethality	
9.*	Doses tested include a NOEL.	
10. 🔀	Individual daily observations. Individual body weights. Individual or cage food consumption.	
11. 🔀	Individual body weights.	
12	Individual or cage food consumption.	
13.*	Individual necropsy not required.	
14. 🚾	Histopathology performed on all animals. Tissue to be fixed in situ using whole anim	al
	perfusion techniques. At least three sections of each of the following tissues:	•
	brain, including medulla oblongata	
	spinal cord; upper cervical, mid-thoracic and lumbro-sacral regions	
	rio ubial nerve; proximal regions and branches — thought no district lev	whiches
	sciatic perve	iameni of

DRAFT Subdivision F Guideline Ref. No. 83-1 Page 29 of November 7, 1989

83-1 Chronic Feeding in the Rodent and Nonrodent

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?:

1/	Technical form of the active ingredi	ent tested.	
2 —	At least 20 rodents or 4 nonrodents/sex/group (3 test groups and control group).		
3	Dosing duration in rodents minimum 12 month nonfood use, 24 months food use; in		
<u>-</u>	nonrodents minimum 12 months ¹ .	10 LOLIG HOLIOSO LO, 01 LIONE 1000 LO, L	
4. no		v at high dose but no lethality in nonrodents or a limit	
	dose if nontoxic (1,000 mg/kg).	y at high dose but no lethality in nonrodents or a limit death at HDT	
5. • , ₩	Doses tested include a NOEL. 10	widote whichers platous con-	
6. ru	Analysis for test material stability, h	n. st pertest and at term) control and high dose.	
7.	Individual daily observations.		
8	individual body weights.		
9. V	Individual or cage food consumption	a.	
10.	Opthalmoscopic examination (at lea	st pertest and at term) control and high dose.	
11.	Clinical pathology data for all nonn	odents and at least 10 rodents/group consisting of 12, 13	
	& 14.		
13.	Hematology at 6 month intervals co	onsisting of at least;	
	Erythrocyte count	Leucocyte count	
	Hemoglobin	Differential count	
_	- Hematocrit	Platelet count (or clotting measure)	
14 🗸	Clinical chemistry at 6 month inter-		
	Alkaline phosphatase	Total Protein	
	Aspartate aminotransferase	Albumin	
	• 100 Creatinine kinese	Urea	
	no Lectic dehydrogenase	Inorganic phosphate	
	Glucose	<u>⊘</u> Calcium	
	Bilirubin	Potassium	
	Cholesterol	Sodium	
	• <u>/~</u> Creatinine	*no Chloride	
15	Urinalysis at 6 month intervals cons		
	™_ Blood	170 Total bilirubin	
	Protein	Urobilirubin	
	Ketone bodies	Sediment	
	Appearance	Specific gravity (osmolality)	
	Glucose	Volume	
16.	Individual necropsy of all animals.		
17.		sues performed on all nonrodents and rodents, all control	
		that died or were killed on study, all gross lesions on all	
		is and lungs, liver and kidneys on all other animals.	

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೯೪೮	bone marrow	kidneys†
caecum	liver†	esophagus
<u>⊘</u> colon	lungt	ovaries†
duodenum	lymph nodes	no oviduct
brain†	stomach	pancreas
skin	mammary gland	<u>ਅਹ</u> rectum
beart t	spleen†	spinal cord (3x)
(a (a)	musculature	thyroid / parathyroids
pituitary	epididymis	salivary glands
ileum	adrenais†	thymus
trachea	uterus	urinary bladder
		•

† organs to be weighed

Six month dog studies may be acceptable. (?)

3/404 CAL/C/340

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83-2 Oncogenicity in Rats of Mice

ACCEPTANCE CRITERIA

1Technical form of the active ingredient tested.	
2 At least 50 animals/sex/group (3 test groups and control group).	
3. Oosing duration is at least 18 months for mice and 24 months for	rats.
4. Number of survivors in any group does not fall below 50% at 15:	months for mice, 18 months
for rats or 25% at 18 months for mice, 24 months for rats.	
5.‡ Doses tested include an MTD or limit dose if nontoxic (1.	,000 mg/kg).
6.*110 Doses tested include a NOEL for systematic effects.	
7.* 115 Analysis for test material stability, homogeneity and conce	ntration in dosing medium
8Individual daily observations.	· de tour
9Individual body weights.	
9. Individual body weights. 10. Individual or cage food consumption. 11. Individual necropsy of all animals.	
	•
12. 100 Blood smear from 10 animals/sex/dose at 12 and 18 month	
count high dose and controls, all other doses if high dose	
13. (19) Histopathology of the following tissues performed on all i	
control and high dose animals, all animals that died or w	
lesions on all animals, target organs on all animals and lu	ings, liver and kidneys on all
other animals.	
v aorta v jejunum v peripheral nerve	histopath inly
eyes bone marrow kidneys†	
caecum liver† esophagus	gross lesure were parent for 1000 organs
colon lung† ovaries†	. gross lexure were
duodenum lymph nodes / 100 oviduct	1
brain† stomach pancreas	1) with
skin mammary gland rectum	cryans
heart† spicen† spinal cord (3x) testes† musculature thyroid / parathyro	U
	ids
picturary epicioyms strivery grands	
ileum adrenais† thymus	
trachen uterus urinary bladder	
t organs to be weighed no organs weighed	

‡ The position document entitled "Selection of a Maximum Tolerated Dose (MTD) in Oncogenicity Studies (EPA No. 540/09-88-003) stated EPA's criteria for determining if an oncongenicity study has been adequately performed in terms of doses-tested. However OPP is also aware that older oncogenicity studies, upon initial review or re-review, may have been tested at doses lower than the predicted MTD. In the event that such testing appears to be at doses less than the predicted MTD, the Office of Pesticides Program has been reviewing and

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considering the entire weight of the evidence to determine if retesting is necessary. Certain factors which affect the agency's decision to retest include but are not limited to the following: demonstrated oncogenicity in another species, nearness to the apparent MTD, genotoxic effects, structure-activity factors, absolute value of the highest dose tested and metabolic considerations.

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83-3 Teratology Studies

ACCEPTANCE CRITERIA

Rut, mi	,
	Technical form of the active ingredient tested.
200 10	At least 20 litters/dose group for mice, rats or hamsters are available. At least 12 litters
7	/dose group for rabbits are available (three test groups and control group).
3. <u>* </u>	Mose group for rabbits are available (three test groups and control group). At the high dose, maternal effects are reported as significant (or a limit dose is given, 1,000
; ; * ;	mg/kg).
4.00	mg/kg). At the low dose, no developmental toxicity is reported.
	. Planta a disperiencia de la contracta de la compansa del compansa de la compansa de la compansa del compansa de la compansa del compansa de la compansa de la compansa de la compansa del compansa de la compansa del compansa de la compansa de la compansa de la compansa del compansa de la compansa de la compansa de la compansa de la co
00	one day prior to term.
6.	Analysis for test material stability, homogeneity and concentration in dosing medium
7. <u>V V</u>	one day prior to term. Analysis for test material stability, homogeneity and concentration in dosing medium individual daily observations. Individual body weights.
A 7 05	Individual food engagements
10 2	Individual food consumption. Necropsy on all animals Individual stating empires including number of fetal deaths, early and late recomptions.
10. <u></u> 11	Individual uterine examination including number of fetal deaths, early and late resorptions
11. 	and numbers of visible fetures ner ser
12	All ovaries examined to determine number of cornors lutes.
13.	Individual litter weights and/or individual fetal weights per sex/litter.
14. VIV	and numbers of viable fetuses per sex. All ovaries examined to determine number of corpora lutea. Individual litter weights and/or individual fetal weights per sex/litter. Individual fetus external examination.
15. <u>~ 7</u> 4	Individual fetus skeletal examination for 1/3 to 1/2 of each litter for rodents and all for all
:	rabbits. 20
16. <u>/ 1</u> 60	Individual fetus soft tissue examination.
. 10	rat feture examined
-48U	Tal ferminen
-# 0 L	rat feture cramened pregnant rabbuts $212/(10 + 11)$ consumption not measured in rabbuts fetus not examined (they examined for first other. and examined for visceral abnormalitie)
· B UT	1979 · As liberts
find	consumption not intaressed in the
0,000	Or examined (help examined for fear
each	ferris () () () () () () () () () (
-file	examined for violence assistant
l/	•

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83-4 Reproduction

· , at)

ACCEPTANCE CRITERIA

3 generatum

Does your study meet the following acceptance criteria?:

Technical form of the active ingredient tested. At least 20 males and sufficient females to yield 20 pregnant Mose group 2 <u>no</u> At least 3 dose groups and a control. <u> հ 3. Ո</u>շ At the high dose, parental toxicity is observed (or a limit dose is given, 1,000 mg/kg/day). 4. <u>10.2.</u> 5.•no At the low dose, no reproductive effects are observed. Analysis for test material stability, homogeneity and concentration in dosing medium P₁ animals 8 weeks old at the start of the study. Dosing is continuous starting with the P₁ animals until an individual animal is sacrificed. Mating is I male to I female. The mating period is not more than 3 weeks. At least two generations are bred. Individual daily observations. Individual body weights. Individual food consumption. Individual litter observations. Individual litter weights (pup weights) at birth and on days 4, 7 (optional), 14 and 21 . (4.4) 124 16. <u>no</u> 17. 00 Sacrifice schedule, all mating males immediately after last mating, all breeding females immediately after weaning last litter, all animals not used for breeding immediately after wearing termination schedule, not reported 18.* 🗸 Necropsy on all animals Histopathology of reproductive organs from all animals on the high dose and control P, and F₁ animals selected for mating. Animals from all other dosing groups if histological effects are observed at the high dose. not done for females 20.º no Histopathology of all organs with gross lesions. * 2 studies summanied - first study involved 2 dose groups and -- RBOCKE inhibited at 100 ppm in one study but not measured in the swood study is here HDT was Zoopppm. avidence of affect on mating performance and pregnancy - ages estimated as seeing 4-5wks - male female ration was 1:2 in the first study - douby observation of test animals not spearfied

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83-5 Chronic Feeding/Oncogenicity in the Rat

study F Medods

ACCEPTANCE CRITERIA

Does was	r study meet the following acceptance criteria?:
	new account and any account and account account account and account account account account and account account account account account and account accoun
1	Technical form of the active ingredient tested.
2 (2)2	At least 50 rats/sex/group (3 test groups and control group). 48 rads issue i pap
3.	Dosing duration is at least 24 months.
4. <u> </u>	Number of survivors in any group does not fall below 50% at 18 months or 25% at 24
	months.
5.7	Doses lested include an MTD or limit dose if nontoxic (1000 mg/kg).
<u> </u>	Doses tested include an MTD or limit dose if nontoxic (1000 mg/kg). Doses tested include a NOEL. The dose produced depression on plassing the limit dose produced depression on plassing the land the production of the limit dose produced depression on plassing the land to the production of the produc
1. <u>.ma</u>	Analysis for test material stability, nomogeneity and concentration in dosing medium
<u> </u>	Individual daily observations.
10	Individual or case food consumption
11.	Individual body weights. Individual or cage food consumption. Opthalmoscopic examination (at least pertest and at term) control and high dose.
12	Clinical pathology data for at least 10 rats/group consisting of 13, 14 & 15
13.	Hematology at 6 month intervals consisting of at least;
	Erythrocyte count Leucocyte count
	Hemoslobin "Differential count
	Hematocrit Platelet count (or clotting measure)
14. <u>^0</u>	
	Alkaline phosphatase Total Protein buly bloom plasm
	Aspartate aminotransferase Albumin
	• Creatinine kinase Urea Che faith
	Lactic dehydrogenase Inorganic phosphate low (5m + 8) per gy
	Glucose Calcium Bilirubin Potassium
	Bilirubin • Potassium
	Cholesterol Sodium
	Creatinine Chloride
15. <u>170</u>	Urinalysis at 6 month intervals consisting of at least; No urinalysis
	Total bilirubin
	Protein Urobilirubin
	Ketone bodies Sediment
	Appearance Specific gravity (osmolality)
1.6	Glucose Volume
17.00	Individual necropsy of all animals. No 8m + 5f / group not subjected to necropsy. Histopathology of the following tissues performed on all nonrodents and rodents, all control
17.(10	and high dose animals, all animals that died or were killed on study, all gross lesions on all
	animals, target organs on all animals and lungs, liver and kidneys on all other animals.
•	AD aorta jejunum peripheral nerve
,	
.	
Criteria m	arked with a * are supplemental and may not be required for every study.

A 7. - homogeneity not formally assessed 17. - Testas and brain collected but not weighed.

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<u> </u>	ମ୍ୟୁଷ <u></u>	bone marrow	_ kidneys†
	caecum	liver† <u>(%</u>	esophagus
	colon	lung† -	ovaries†
	duodenum No	lymph nodes 📉	oviduct
*	brain†	stomach	pancreas
710	skin y vo	mammary gland 📉	rectum
	beart	spicen†	spinal cord (3x)
+	(SIS)	musculature	thyroid / parathyroids
	pituitary	epididymis	salivary glands
	ileum	adrenals	- thymus
	trachea	uterus	urinary bladder

† organs to be weighed.

† The position document entitled "Selection of a Maximum Tolerated Dose (MTD) in Oncogenicity Studies (EPA No. 540/09-88-003) stated EPA's criteria for determining if an oncongenicity study has been adequately performed in terms of doses tested. However OPP is also aware that older oncogenicity studies, upon initial review or re-review, may have been tested at doses lower than the predicted MTD. In the event that such testing appears to be at doses less than the predicted MTD, the Office of Pesticides Program has been reviewing and considering the entire weight of the evidence to determine if retesting is necessary. Certain factors which affect the agency's decision to retest include but are not limited to the following: demonstrated oncogenicity in another species, nearness to the apparent MTD, genotoxic effects, structure-activity factors, absolute value of the highest dose tested and metabolic considerations.

metabolic considerations.

** eyes, Shin, and lymph when, manning glind, muscle

crophagus, oviduet c. I when only examined if grossly abound

frain and fosks not weight

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84-2 Mutagenicity Studies

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?:

General P	lequirements		
1	Technical form of the active ingredient tested.		
2	Negative, solvent and/or vehicle control(s) for the test system.		
3	Positive control(s) for the test system.		
4	Fully identified test system, species, strain, source etc.		
5	Fully described method for maintaining test system.		
6	Fully described method for preparing test environment and administering test compond.		
7	Fully described metabolic activation system, if required.		
8	Determination of maximum and range of concentrations/doses used under test conditions.		
9.•	Determination of maximum and range of concentrations/doses used under test conditions. Criteria for determination of a positive effect.		
Test Speci	fic Requirements		
	Salmonella reverse mutation assay		
1	Minimum of four grains TAGE TAIGO TAIGS and TAIGS6 (alternatives need rationals)		
2	Strain specific positive controls.		
3	Highest concentration limited by toxicity, solubility or 5000 ug/plate.		
4.*	At least 5 different concentrations of test material at adequate intervals.		
5.*	A single positive response confirmed by testing over a narrow range of concentrations.		
6.*	Strain specific positive controls. Highest concentration limited by toxicity, solubility or 5000 ug/plate. At least 5 different concentrations of test material at adequate intervals. A single positive response confirmed by testing over a narrow range of concentrations. At least three plates experimental point. Gene mutation in somatic cells in culture		
	Gene mutation in sometic cells in culture		
1.	Highest concentration limited by toxicity (10-20% relative survival), solubility or 5000 ug/ml. At least 4 different concentrations of test material to yield a concentration related toxic		
2.	At least 4 different concentrations of test material to yield a concentration related toxic		
	effect		
3.	Determination of the number of cell cultures used.		
	In vitro mammalian evioenetics		
	Highest concentration limited by toxicity (e.g. reduced mitotic activity; alteration of cell cycle;		
·· —	cytotomicity), solubility or 5000 ug/ml.		
2 •	Multiple constrained med to define the conserve		
<u>-</u>	Multiple concentrations used to define the response. At least two independent cultures for each experimental point. Determination of culture harvest time.		
3	The emination of culture beauty since		
• —	Lettermination of centers arrest time.		
	In vivo mammalian cytosenetics - done marrow		
1	At least 5 male and 5 female animals per experimental group.		
2	Highest dose limited by toxicity or 5000 mg/kg.		
3	In vivo mammalian cytosenetics - bone marrow At least 5 male and 5 female animals per experimental group. Highest dose limited by toxicity or 5000 mg/kg. Determination of sampling times. Aberrations: a) one treatment - 3 times in range of 6-48 hours after treatment adequately.		
	residence of the entire of the residence and the entire sections,		
	spaced with central sample at 24 hour (may be altered based on cell cycle time). b)		
	repeated treatments - samples taken 6 and 24 hours after last treatment (may be		

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	altered based on cell cycle time).
	Micronucleus, Samples taken 3 times, starting not earlier than 12 hours after the last
	treatment and at appropriate intervals following the first sample, but not beyond 72 hours.
4	Micronucleus assay, at least 1000 polychromatic erythrocytes/animal scored. Ratio of poly to normochromatic determined by counting 200-1000 erythrocytes (1000 OECD).
	Rodent dominant lethal assay
1	Sufficient number of dosed males to provide a minimum of 30 pregnant females per mating interval.
2	Concurrent positive control or results from positive control conducted within 12 months in same laboratory with same strain.
3	Highest dose produced toxicity or 5000 mg/kg.
4.	Sampling or exposure over entire spermatogenesis cycle of dosed males (8 weeks mice, 10 weeks rats)
	Any mutagenicity test with suggestive or greater positive results/activity shall be submitted requrdless of missing essential items.

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85-1 Metabolism Studies

ACCEPTANCE CRITERIA

Does your	stady meet me tonowing acceptance	e cultum:	
1	Analytically pure grade of the activ	ve ingredient.	
2	Isotopically labeled in the core of	the molecule and/or significant portions thereof. -OR-	
, 3 ,	Analytical procedures sufficiently s	pecific and sensitive to identify the test substance.	
4	Young adult rats. Other mammalia	in species may be used for specific purposes.	
5	Five male and five female rats for	each dose, 4 if following OECD protocol.	
6	Two doses, the low to be without of signs but not severe effects or mor	each dose, 4 if following OECD protocol. effect and the high to produce toxic or pharmacological tality.	
7.*	Dosing group A, single low dose by intravenous route (not required if insoluble in water or		
8	Dosing group B, single low dose b	y oral route.	
9	normal saline). Dosing group B, single low dose by oral route. Dosing group C, 14 consecutive daily low dose of the unlabeled test material by oral route followed by a single low dose of the labeled test material. Dosing group D, single high dose by oral route.		
10.	South Fresh Strange with the	of citt icere.	
11.	Collect individually all urine, feces and expired air for 7 days after labeled dose or until 90+ percent of the dose is excreted (whichever occurs first). Expired air not required if a pilot		
	study shows no excretion in 24 hor		
12	For dosing groups B, C and D, qu	antity of label in the following tissues and organs;	
	bone	liver	
	brain	lung	
	fa t	lung blood	
•	testes beart kidney	muscle	
	beart	spiecn	
	kidney	residual carcass	
	tissues showing pathology in	this or prior studies	
For all do	sing groups:		
13.	Quantities of label in urine, feces	and expired air (if detected in preliminary study) at	
	appropriate intervals (e.g. 4, 8, 12	and 24 hours, 1.5, 2, 3, 4, 5, 6 and 7 days.	
14.	Qualitative analysis of urine and f	eces to detect metabolism and identify metabolites (pooled	
	urine and feces by dosing group m	lay be used).	
	he metabolism data requirement ma	ry be filled in part. For example performing the analysis on at for that dose.	

Primary eye irritation/rabbit

PHASE FOUR REVIEW (NOTE: This only contains additions and changes from the phase 2 response.) Pesticide: Chemical #/Case#: PIRIMIPHOS - METRYL Transmitted to HED on: Tox, Chem #: Sponsor: IC CRM: Phone#: Branch: Tox-I Reviewer: Completed: 12/10/90 Concurrence: Are there any changes from the reviews in phase 2? NO (See below) Response, by Guideline a di marini Guideline #: 81-1 Acute oral/rat MRID Study # Discussion/Recommendation: Guideline #: 81-2 Acute dermal/rabbit Study # Discussion/Recommendation: Guideline #: 81-3 Acute inhalation/rat MRID_____ Study #__ Discussion/Recommendation:

Guideline #: 81-4

Discussion/Recommendation:

Guideline #: 81-5	Primary dermal irritation/rabbit
MRID Study # Discussion/Recommendation:	
Guideline #: 81-6 MRID Study # Discussion/Recommendation:	Dermal sensitization/Guinea Pig
Guideline #: 81-7	Acute delayed neurotoxicity/hen
MRID Study # Discussion/Recommendation:	· item
Guideline #: 82-1a MRID Study # Discussion/Recommendation:	90-day feeding/rodent
Guideline #: 82-1b MRID Study # Discussion/Recommendation:	90-day feedubg/nonrodent
Guideline #: 82-2 MRID Study # Discussion/Recommendation:	21 Day dermal/rodent/rabbit

Guideline #: 82-3		90-day dermal/rodent
MRIDStudy # Discussion/Recommendation:		· ·
Guideline #: 82-4		90-Day inhalation/rat
MRID Study # Discussion/Recommendation		
Guideline #: 82-5		90-day neurotoxicity
MRIDStudy # Discussion/Recommendation:		• of comm.
Guideline #: 83-la	, s	Chronic toxicity/rodent
MRID Study # Discussion/Recommendation:		
Guideline #: 83-1b		Chronic toxicity/nonrodent
MRIDStudy # Discussion/Recommendation:		
	•	
Guideline #: 83-2a		Oncogenicity/rat
MRIDStudy #		

Oncogenicity/mouse Guideline #: 83-2b Study #_ MRID Discussion/Recommendation: Guideline #: 83-3a Teratology/rat Study #_ Discussion/Recommendation: Guideline #: 83-3b Teratology/rabbit Study #__ MRID Discussion/Recommendation: Guideline #: 83-4 Two-generation reproduction/rat Study #_ Discussion/Recommendation: Mutagenicity/Ames Guideline #: 84-2a MRID (92147-020) Study # YV 1226 (Rpt, CTL/P/962) Discussion/Recommendation: Phase-3 Summary Response appears to be "picceptable for a 1989 study Discussion/Recommendation: Mutagenicity/Struct. Chromosomal Aberration

///
/ Dominant Lethal - mu Guideline #: 84-2b MRID 41556302 study # CTL/C/291 Discussion/Recommendation: Phase 3 Summary Response alludes to major deficiencies in this 1975 assay which would render it unacceptable. * Not certain technical was tested; details of animal care/husbandry about; no indication top dose was toxic

•	
-2	Gene mutation in
Guideline #: 84-X	Other genetoxic effects
MRID 41556303 Study # CTL/C/1437 Discussion/Recommendation: This Phase 3 indicates this 1985 array was carefred which would readly	Summary Leopens
10 1 1604	mend out worder
criteria which would render	it exceptable.
·	
Guideline #: 85-1	<u>Metabolism</u>
MRID Study # Discussion/Recommendation:	
Guideline #: 85-2	Dermal penetration
MRIDStudy # Discussion/Recommendation:	• A tour .
•	·
Guideline #: 86-1	Domestic animal safety
MRID Study #	•.
MRID Study # Discussion/Recommendation:	

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81-1 Acute Oral Toxicity in the Rat

ACCEPTANCE CRITERIA

MRID#S 00 126257, 00164523

1. 100	Technical form of the active ingredient tested. (for reregistration only)
2.*	At least 5 young adult rats/sex/group
3	Dosing, single oral.
4.	Vehicle control if other than water.
5	Doses tested, sufficient to determine a toxicity category or a limit dose (5000 mg/kg).
6	Individual observations for the entire day of dosing.
7	Observation period to last at least 14 days, or until all test animals appear normal whichever
	is longer.
8	Individual daily observations.
9.*	Individual body weights.
10.*	Gross necropsy on all animals.

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81-2 Acute Dermal Toxicity in the Rat, Rabbit or Guinea Pig

ACCEPTANCE CRITERIA

MR10#500126257 and 00164523

1. <u>100</u>	Technical form of the active ingredient tested. (for reregistration only)
2.*	At least 5 animals/sex/group
3.*	Rats 200-300 gm, rabbits 2.0-3.0 kg or guinea pigs 350-450 gm.
4	Dosing, single dermal.
5	Dosing duration at least 24 hours.
6.*	Vehicle control, only if toxicity of vehicle is unknown.
7.	Doses tested, sufficient to determine a toxicity category or a firmit dose (2000 mg/kg).
8	Application site clipped or shaved at least 24 hours before dosing
9	Application site at least 10% of body surface area.
10	Application site covered with a porous nonirritating cover to retain test material and to
	prevent ingestion.
11	Individual observations for the entire day of dosing.
12	Observation period to last at least 14 days, or until all test animals appear normal whichever
	is longer.
13	Individual daily observations.
14.*	Individual body weights.
15.•	Gross necropsy on all animals.

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81-3 Acute Inhalation Toxicity in the Rat

ACCEPTANCE CRITERIA

MRID# 00126258

1. <u>∧ ≎</u>	Technical form of the active ingredient tested. (for reregistration only)
2	Product is a gas, a solid which may produce a significant vapor hazard based on toxicity and
	expected use or contains particles of inhalable size for man (aerodynamic diameter 15 um or
	less).
3.*	At least 5 young adult rats/sex/group
4.*	Dosing, at least 4 hours by inhalation.
4.* 5.*	Chamber air flow dynamic, at least 10 air changes/hour, at least 19% oxygen content.
6	Chamber temperature, 22° C (+2°), relative humidity 40-60%.
7.	Monitor rate of air flow
8	Monitor actual concentrations of test material in breathing zone.
9	Monitor aerodynamic particle size for aerosols.
10.	Doses tested, sufficient to determine a toxicity catagory or a limit dose (5 mg/L actual
	concentration of respirable substance).
1	Individual observations for the entire day of dosing.
2.	Observation period to last at least 14 days, or until all test animals appear normal whichever
	is longer.
3	Individual daily observations.
	Individual body weights.
5.•	Gross necropsy on all animals.

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81-4 Primary Eye Irritation in the Rabbit

ACCEPTANCE CRITERIA

1 RID\$ 00126257 and 00164524

Does y	your	study	meet	the	following	acceptance	criteria?
--------	------	-------	------	-----	-----------	------------	-----------

Technical form of the active ingredient tested. (for reregistration only)
Study not required if material is corrosive, causes severe dermal irritation or has a pH of <
$2 \text{ or } \ge 11.5.$
6 adult rabbits
Dosing, instillation into the conjunctival sac of one eye per animal.
Dose, 0.1 ml if a liquid; 0.1 ml or not more than 100 mg if a solid, paste or particulate substance.
Solid or granular test material ground to a fine dust.
Eyes not washed for at least 24 hours.
Eyes examined and graded for irritation before dosing and at 1, 24, 48 and 72 hr, then daily
until eyes are normal or 21 days (whichever is shorter).
Individual observations for the entire day of dosing.
Individual daily observations.

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81-5 Primary Dermal Irritation Study ACCEPTANCE CRITERIA

MRID#5 00 126257 and 00164524

Technical form of the active ingredient tested. (for reregistration only)
Study not required if material is corrosive or has a pH of ≤ 2 or ≥ 11.5 .
6 adult animals.
Dosing, single dermal.
Dosing duration 4 hours.
Application site shaved or clipped at least 24 hour prior to dosing.
Application site approximately 6 cm ² .
Application site covered with a gauze patch held in place with nonirritating tape
Material removed, washed with water, without trauma to application site
Application site examined and graded for irritation at 1, 24, 48 and 72 hr, then daily until
normal or 14 days (whichever is shorter).
Individual observations for the entire day of dosing.
Individual daily observations.

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81-6 Dermal Sensitization in the Guinea Pig

ACCEPTANCE CRITERIA

MRID	601	29341

Does y	our study	meet the	following	acceptance	criteria?:
--------	-----------	----------	-----------	------------	------------

•	
1. 2	Technical form of the active ingredient tested. (for reregistration only) Study not required if material is corrosive or has a pH of ≤ 2 or ≥ 11.5 . One of the following methods is utilized;
<u> - </u>	Freund's complete adjuvant test
	Guinea pig maximization test
	Split adjuvant technique
	Buehler test
-	Open epicutaneous test
	Maur optimization test
	Footpad technique in guinea pig
1	Other test accepted by OECD (specify)
4. 🗸	Complete description of test
5. <u>NO</u> 6. <u>?.</u>	Reference for test.
6. <u>?. </u>	Test followed essentially as described in reference document.
7. NO	Positive control included.

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81-7 Acute Neurotoxicity in the Hen

1.1.4	Study performed on an organophosphate cholinesterase inhibiting compound.
21/	Technical form of the active ingredient tested.
3.∜+	Positive control utilized.
4.4_+	Species utilized, domestic laying hen 8-14 months of age.
	Dosing oral by gavage or capsule (dermal or inhalation may be used).
	An acute oral LD ₅₀ is determined.
	Dose tested equal to an acute oral LD ₃₀ or a limit test of 5000 mg/kg.
	Dosed animals may be protected with atropine and/or 2-PAM.
	Sufficient test animals so that at least 6 survive.
	Negative (vehicle) control group of at least 6 hens
	Positive control of at least 4 hens. (if used)
	O Test dose repeated if no signs of delayed neurotoxicity observed by 21 days after dosing.
	Observation period 21 days after each dose.
	Individual daily observations.
	Individual body weights.
16.*7	
17.100 ;	Histopathology performed on all animals. Tissue to be fixed in situ using whole animal
	perfusion techniques. At least three sections of each of the following tissues:

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82-1 Subchronic Feeding in the Rodent and Nonrodent

ACCEPTANCE CRITERIA Dost MAID#/Acr # NA

Rot	V MRIO#/Acct NA	Dog +	MAID#/Acc#NA
Does you	r study meet the following acceptai	nce criteria?:	
2. 1	Dosing duration daily for 90-days Doses tested include signs of tox	ents/sex/group or 5 days/we	(3 test groups and control group).
6. 7.	dose if nontoxic (1000 mg/kg). Doses tested include a NOEL. Analysis for test material stability Individual daily observations. Individual body weights.	y, homogenei	ity and concentration in dosing medium
9. 7 ? 10.•?	Individual or cage food consump Opthalmoscopic examination (at Clinical pathology data of 12 & and at termination for nonrodent	least pretest 13 at termina	and at term) control and high dose. ation for rodents, before, monthly or midway
12 / #	Hematology. Erythrocyte count Hemoglobin Hematocrit Clinical chemistry.	• Þ	eucocyte count Differential count latelet count (or clotting measure)
	Alkaline phosphatase Aspartate aminotransferase Creatinine kinase Lactic debutrosenase	^	otal Protein Libumin Irea norganic phosphate
	Glucose Bilirubin Cholesterol Creatinine		alcium otassium odium Chloride
14.° <u>№ </u>	Blood Protein Ketone bodies	To	or observed activity. As scheduled in 11. Otal bilirubin Jrobilirubin ediment
15.?? 16. ?	Appearance Glucose Individual necropsy of all animal Histopathology of the following the dose animals all animal	s. Lissues perfoi	pecific gravity (osmolality) /olume rmed on all nonrodents and rodents, all control or were killed on study, all gross lesions on all
			es. liver and kidneys on all other animals.

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aorta	jejunum	peripheral nerve
eyes	bone marrow	kidneys†
caecum	liver†	esophagus
colon	lung†	ovaries†
duodenum	lymph nodes	oviduct
brain†	stomach	pancreas
skin	mammary gland	rectum
heart†	spleen†	spinal cord (3x)
testes†	musculature	thyroid / parathyroid
pituitary	epididymis	salivary glands
ileum	adrenals†	thymus
trachea	uterus	urinary bladder
† organs to be weigh	hed	

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82-2 Repeated Dose Dermal Toxicity (21-day) in the Rat, Rabbit or Guinea Pig

ACCEPTANCE CRITERIA

MRID# 00129342

noce los	r study meet the following acceptance	chare:				
1	Technical form of the active ingredi					
2 🚣	At least 5 animals/sex/group (3 test groups and control group).					
3. \frac{1}{7} 5. \frac{1}{7}	Dosing duration at least 6 hour/day for 21 days or 5 days/week for 3 weeks.					
4 7	Application site at least 10% of boo					
	lethality or a limit dose (1000mg/kg)	y at high dose, no or minimal dermal irritation, minimal) if nontoxic.				
6. NO	Doses tested include a NOEL.					
7	Individual daily observations.					
8. 7	Individual body weights.					
9. 📆	Individual or cage food consumption	1.				
7. 7 8. 7 9. 7 10. 7	Clinical pathology data of 11 & 12					
11.	Hematology.	,				
	Erythrocyte count	Leucocyte count				
	Hemoglobin	Differential count				
,	✓ Hematocrit	Platelet count (or clotting measure)				
12.	Clinical chemistry.	,				
	Alkaline phosphatase	V. Total Protein				
	✓ Aspartate aminotransferase	Albumin				
	Creatinine kinase	✓ Urea				
	Lactic dehydrogenase	Inorganic phosphate				
	✓ Glucose	Calcium				
	Bilirubin	Potassium				
	Cholesterol	✓ Sodium				
	* Creatinine	Chloride				
12 •		expected or observed activity. As scheduled in 10.				
	Blood	Total bilirubin				
	Protein	Urobilirubin				
	Ketone bodies					
		Sediment				
	Appearance	Specific gravity (osmolality)				
	Glucose	• Volume				
14. 	Individual necropsy of all animals.					
I.S		ntrol and high dose animals, all animals that died or were				
	killed on study consisting of all gros	is lesions on all animals, target organs on all animals (to				
	determine a NOEL), and skin (north	nal and treated) lungs, liver and kidneys.				

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82-3 Repeated Dose Dermal Toxicity (90-day) in the Rat, Rabbit or Guinea Pig

ACCEPTANCE CRITERIA

DOG JOU	is study meet the following acceptance of	ancar:				
1	Technical form of the active ingredien	nt tested.				
2	At least 10 animals/sex/group (3 test groups and control group).					
3	Dosing duration at least 6 hour/day d	Dosing duration at least 6 hour/day daily for 90 days or 5 days/week for 13 weeks.				
4.		Application site at least 10% of body surface area.				
5	Doses tested include signs of toxicity	at high dose, no or minimal dermal irritation, minimal				
	lethality or a limit dose (1000mg/kg)					
6.*						
7.	Individual daily observations.					
8	Individual body weights.					
9	Individual body weights. Individual or cage food consumption.					
10.•	Opthalmoscopic examination (at least	pretest and at term) control and high dose. all animals at termination.				
11	Clinical pathology data of 12 & 13 in	all animals at termination.				
12.	Hematology.					
	Erythrocyte count	Leucocyte count Differential count				
	Hemoglobin	• Differential count				
	Hematocrit	Platelet count (or clotting measure)				
13	Clinical chemistry.					
	Alkaline phosphatase	Total Protein				
	Aspartate aminotransferase	Albumin				
•	* Creatinine kinase	Urea				
	Lactic dehydrogenase	Inorganic phosphate				
	Glucose	Calcium				
	Bilirubin	Potessium				
	Cholesterol	Sodium				
	" Creatinine	· Chioride				
14.*	Urinalysis, only when indicated by ex	pected or observed activity. As scheduled in 11.				
	Blood	Total bilirubin				
	Proteia	• Urobilirubin				
	Ketone bodies	Sediment				
	Appearance	Specific gravity (osmolality)				
	Glucose	• Volume				
15	Individual necropsy of all animals.					
16	Histopathology of the following tissue	es performed on all nonrodents and rodents, all control				
	and high dose animals, all animals th	at died or were killed on study, all gross lesions on all				
	animals, target organs on all animals	and lungs, liver and kidneys on all other animals.				
	sorta jejunum					
	eyes bone man					

Criteria marked with a * are supplemental and may not be required for every study.

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caecum colon duodenum	liver† lung† lymph nodes	esophagus ovaries†
brain†	stomach mammary gland	pancreas rectum
heart†	spleen† musculature	spinal cord (3x) thyroid / parathyroids
pituitary	epididymis adrenals†	salivary glands thymus
trachea	uterus	urinary bladder
† organs to be weight	ed	

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82-4 Subchronic Inhalation Toxicity (90-day) in the Rat

ACCEPTANCE CRITERIA

Does your	study meet the following acceptance of	riteria?:				
1	Technical form of the active ingredien	it tested. (for reregistration only)				
	Product is a gas, a solid which may produce a significant vapor hazard based on toxicity and					
	expected use or contains particles of inhalable size for man (aerodynamic diameter 15 um of					
_	less).					
3	At least 10 young adult rats/sex/group					
4	Dosing, 6 hours per day, 5 days per week for 13 weeks.					
J	Chambas sis flow America at least 10	uring dosing. air changes/hour, at least 19% oxygen content.				
0.*	Chamber air now dynamic, at least 10	all changes/nour, at least 1976 oxygen content.				
/	Chamber temperature, 22° C $(\pm 2^\circ)$, real Alternatively, oro-nasal or head only	ciative numidity 40-00%.				
		exposures may be used.				
	Monitor rate of air flow, Monitor actual concentrations of test	material in breathing sone				
10	Monitor aerodynamic particle size for					
11	Individual daily observations.	aciosob.				
13	Individual body weights.					
14	Individual or cage food consumption.					
15.	Onthalmosconic examination (at least	pretest and at term) control and high dose.				
16.	Clinical pathology data of 17 & 18 in	all animals at termination				
	Hematology.	411				
· · ·	•	Leucocyte count				
	Hemoglobin	Leucocyte count Differential count				
	Hematocrit	Platelet count (or clotting measure)				
18.	Clinical chemistry.					
	Alkaline phosphatase	Total Protein				
	Aspartate aminotransferase	Albumin				
	Creatinine kinase	Urea				
	Lactic dehydrogenase	Inorganic phosphate				
	Glacose	Calcium				
	Bilirubin	Potassium				
	Cholesterol	Sodium				
	· Creatinine	Caloride				
19.*		pected or observed activity. As scheduled in 16.				
	Blood	Total bilirubin				
	Protein	Urobilirubin				
	Ketone bodies	Sediment				
	Appearance	Specific gravity (osmolality)				
	Glucose	Volume				

Criteria marked with a * are supplemental and may not be required for every study.

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	s on all animals and lui	or were killed on study, all gross lesions on a ngs, liver and kidneys on all other animals.
aorta	jejunum	peripheral nerve
c yes	bone marrow	kidneys†
caecum	liver†	esophagus
∞lon	lung†	ovaries†
duodenum	lymph nodes	oviduct
brain†	stomach	pancreas
skin	mammary gland	rectum
beart†	spicen†	spinal cord (3x)
testes†	musculature	thyroid / parathyroids
pituitary	epididymis	salivary glands
ileum	adrenals†	thymus
trachea	uterus	urinary bladder

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82-5 Subchronic Neurotoxicity (90-day) in the Hen

ACCEPTANCE CRITERIA

MRID#00126254

1	Study performed on an organophosphate cholinesterase inhibiting compound.
2.	Technical form of the active ingredient tested.
3. 🔽	Technical form of the active ingredient tested. Positive control utilized. (recommended but optional) Species utilized, domestic laying hen 8-14 months of age. At least 10 animals/sex/group [3 test groups, a positive control (optional) and a negative
4. 🗸	Species utilized, domestic laying hen 8-14 months of age.
5.	At least 10 animals/sex/group [3 test groups, a positive control (optional) and a negative
	(vehicle) control group].
6. <u>/</u> /	Dosing duration at least daily for 90 days or 5 days/week for 13 weeks.
7.	Date sents and sense as around (damed as inhalation may be accounted)
8. 🔀	Doses tested include signs of toxicity at high dose, no or minimal lethality Doses tested include a NOEL. Individual daily observations. Individual body weights. Individual or cage food consumption. Individual necropsy not required. Historical particular and an all parisons. Tissue to be found in sign parisons where an include a parison to be found in sign parisons.
9.*	Doses tested include a NOEL.
10. 7-	Individual daily observations.
11. <u>7.</u>	Individual body weights.
12. 7.	individual or cage food consumption.
13.*	Individual necropsy not required.
14. NO	Histopathology performed on all animals. Tissue to be fixed in situ using whole animal
	perfusion techniques. At least three sections of each of the following tissues:
. •	brain, including medulla oblongata
	spinal cord; upper cervical, mid-thoracic and lumbro-sacral regions
	tibial nerve; proximal regions and branches
	sciatic perve

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83-1 Chronic Feeding in the Rodent and Nonrodent

ACCEPTANCE CRITERIA

Norro	bent MRID# /ACC# NA 1	DER study ? Hunleyton 3/11/73
Does was	r study meet the following acceptance	evitaria?
•	•	
1. √	Technical form of the active ingred	ient tested. s/sex/group (3 test groups and control group). m 12 month nonfood use, 24 months food use; in ty at high dose but no lethality in nonrodents or a limit
2. 🔽	At least 20 rodents or 4 nonrodents	s/sex/group (3 test groups and control group).
3. 🔽	Dosing duration in rodents minimu	m 12 month nonfood use, 24 months food use; in
7	nonrodents minimum 12 months ¹ .	•
4	Doses tested include signs of toxicit	ty at high dose but no lethality in nonrodents or a limit homogeneity and concentration in dosing medium n. ust pertest and at term) control and high dose. odents and at least 10 rodents/group consisting of 12, 13
e a Ni	dose if nontoxic (1,000 mg/kg).	
5.0 100	Applying for test material stability	homogeneity and concentration in desire medium
7	Individual daily observations	homogeneity and concentration in dosing medium
8 7	Individual hady weights.	
9. 📆	Individual or case food consumptio	Π _σ
10.	Opthalmoscopic examination (at lea	ast pertest and at term) control and high dose.
11. 📆	Clinical pathology data for all nonr	odents and at least 10 rodents/group consisting of 12, 13
	& 14.	
13	Hematology at 6 month intervals of	onsisting of at least;
	Erythrocyte count	Leucocyte count Differential count
•	Hemoglobin	• Differential count
7	Hematocrit	Platelet count (or clotting measure)
14	Clinical chemistry at 6 month inter	
	Alkaline phosphatase	Total Protein
•	Aspartate aminotransferase Creatinine kinase	Albumin
	Creatinine kinase	Urea
	Lactic dehydrogenase	Inorganic phosphate
	Glucose	Calcium
	Bilirubin	Potassium Sodium
	Cholesterol Creatinine	* Chloride
15	Urinalysis at 6 month intervals con	cicting of at least:
	Blood	Total bilirubin
	Protein	• Urobilirubin
	Ketone bodies	Sediment
	Appearance	Specific gravity (osmolality)
7	. Glucose	Volume
16. <u> </u>	Individual necropsy of all animals.	•
17. 📆	Histopathology of the following tiss	sues performed on all nonrodents and rodents, all control
	and high dose animals, all animals	that died or were killed on study, all gross lesions on all
	animals, target organs on all anima	is and lungs, liver and kidneys on all other animals.

Criteria marked with a * are supplemental and may not be required for every study.

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cyes	bone marrow	kidneys†
caecum	liver†	esophagus
colon	lung†	ovaries†
duodenum	lymph nodes	oviduct
brain†	stomach	pancreas
skin	mammary gland	rectum
heart†	spleen†	spinal cord (3x)
testes†	musculature	thyroid / parathyroids
pituitary	epididymis	salivary giands
ileum	adrenals†	thymus
trachea	uterus	urinary bladder
	-	
† organs to be we	ighed	
Six month dog studies may	be acceptable. (?)	

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83-2 Oncogenicity in Rats or Mice

ACCEPTANCE CRITERIA

Mile	MRID#/Acc#	NA DER of	which #	ICI 34	117658 - 7	1/5/76
Technical form of the active ingredient tested. Technical form of the active ingredient tested. To Desire duration is at least 18 months for mice and 24 months for rats. Number of survivors in any group does not fall below 50% at 15 months for mice, 18 months for rats or 25% at 18 months for mice, 24 months for rats. Doses tested include an MTD or limit dose if nontoxic (1,000 mg/kg). Doses tested include a NOEL for systematic effects. Analysis for test material stability, homogeneity and concentration in dosing medium individual daily observations. Individual or cage food consumption. Individual necropsy of all animals. Blood smear from 10 animals/sex/dose at 12 and 18 months and termination. Differential count high dose and controls, all other doses if high dose shows pathology. Histopathology of the following tissues performed on all interim sacrifice animals, all						
		animais, target or				on study, all gross and kidneys on all
_	aorta eyes caecum colon duodenum brain skin heart testes†	jejunum bone marrow liver† lung† stomach mammary gland spicen† musculature	des pan	pheral nerviceys† chagus ries† creas um al cord (3x oid / parati	ı ·	
† org	pituitary ileum itraches ans to be weigh	uterus	saliv	vary glands uary bladder	•	·

‡ The position document entitled "Selection of a Maximum Tolerated Dose (MTD) in Oncogenicity Studies (EPA No. 540/09-88-003) stated EPA's criteria for determining if an oncongenicity study has been adequately performed in terms of doses tested. However OPP is also aware that older oncogenicity studies, upon initial review or re-review, may have been tested at doses lower than the predicted MTD. In the event that such testing appears to be at doses less than the predicted MTD, the Office of Pesticides Program has been reviewing and

Criteria marked with a * are supplemental and may not be required for every study.

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towar.

considering the entire weight of the evidence to determine if retesting is necessary. Certain factors which affect the agency's decision to retest include but are not limited to the following: demonstrated oncogenicity in another species, nearness to the apparent MTD, genotoxic effects, structure-activity factors, absolute value of the highest dose tested and metabolic considerations.

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(nobbit +) MRID#ACE NA DER Stuf# HO/CTL/P/119B; 7/14

83-3 Teratology Studies

ACCEPTANCE CRITERIA

MRID#00151623(not/)

Does your study meet the following acceptance criteria?:
1
2. At least 20 litters/dose group for mice, rats or hamsters are available. At least 12 litters
/ Mose group for rabbits are available (three test groups and control group).
3. At the high dose, maternal effects are reported as significant (or a limit dose is given, 1,000
mg/kg). 4.* At the low dose, no developmental toxicity is reported.
4.* V That the low dose, no developmental toxicity is reported.
5. $\sqrt{}$ + Dosing duration is at least during the period of major organogenesis, but may extend up to
one day prior to term. 6.* Analysis for test material stability, homogeneity and concentration in dosing medium
6.* Analysis for test material stability, homogeneity and concentration in dosing medium
7. 7. Individual daily observations.
8. 2 ? Individual body weights.
7. 7. 1 Individual daily observations. 8. 7. 7 Individual body weights. 9. 7 Individual food consumption.
10. V Necropsy on all animals
11. 2 Individual uterine examination including number of fetal deaths, early and late resorptions
and numbers of viable fetuses per sex.
and numbers of viable fetuses per sex. 12
13. // Individual litter weights and/or individual fetal weights per sex/litter.
14. Individual fetus external examination.
15 ? Individual fetus skeletal examination for 1/3 to 1/2 of each litter for rodents and all for all
, rabbits.
16. V. Individual fetus soft tissue examination.

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83-4 Reproduction

	ACCEPTANCE CRITERIA	
Rt#1) MR10#	Acc# NA DER atual #547/72/853; 12/7172 (Rat #2 +) MRIO*/Act NA DE r study meet the following acceptance criteria?: (Rat #2 +) MRIO*/Act NA DE	R* B
Does you	r study meet the following acceptance criteria?:	63/7
	Technical form of the active ingredient tested.	
	At least 20 males and sufficient females to yield 20 pregnant /dose group At least 3 dose groups and a control.	
	At the high dose, parental toxicity is observed (or a limit dose is given, 1,000 mg/kg/day).	
	At the low dose, no reproductive effects are observed.	
6.* <u>~</u> ?	Analysis for test material stability, homogeneity and concentration in dosing medium	- tusers
7. <u> </u>	P, animals 8 weeks old at the start of the study.	
8. 7 /	Dosing is continuous starting with the P ₁ animals until an individual animal is sacrificed.	
	- Mating is 1 male to 1 female. The mating period is not more than 3 weeks.	
	The mating period is not more than 5 weeks. At least two generations are bred.	
12. 7	Individual daily observations.	
13. 7. ?	Individual daily observations. Individual body weights.	
14. 7. 4	Individual food consumption.	
15. $\frac{7}{2}$	Individual litter observations.	
16	Individual litter weights (pup weights) at birth and on days 4, 7 (optional), 14 and 21.	
	Sacrifice schedule, all mating males immediately after last mating, all breeding females immediately after weaning last litter, all animals not used for breeding immediately after	
18.* ? ?	minimization wearing and inter, an animals not used for breeding minimization after	
18.*	Necropsy on all animals	
19.•?	Histopathology of reproductive organs from all animals on the high dose and control P ₁ and	
	F ₁ animals selected for mating. Animals from all other dosing groups if histological effects	
2 2 2 2	are observed at the high dose.	
20.•	Histopathology of all organs with gross lesions.	

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83-5 Chronic Feeding/Oncogenicity in the Rat

MOIOH	ACCEPTANCE CRITERIA	
	DER Study HO/IH/P/113; 6/74	
Does you	ar study spect the following acceptance criteria?:	
1. $\frac{}{2}$ $\frac{}{2}$ 3. $\frac{}{2}$	Technical form of the active ingredient tested. At least 50 rats/sex/group (3 test groups and control group). Dosing duration is at least 24 months. Number of survivors in any group does not fall below 50% at 18 months or 25% at 24	
5.‡ / 6.• /	months. Doses tested include an MTD or limit dose if nontoxic (1000 mg/kg). Doses tested include a NOEL. Analysis for test material stability homogeneity and concentration in doring medium.	•
8. 7 9. 7 10. 7	months. Doses tested include an MTD or limit dose if nontoxic (1000 mg/kg). Doses tested include a NOEL. Analysis for test material stability, homogeneity and concentration in dosing medium Individual daily observations. Individual body weights. Individual or cage food consumption. Opthalmoscopic examination (at least pertest and at term) control and high dose. Clinical pathology data for at least 10 rats/group consisting of 13, 14 & 15 Hematology at 6 month intervals consisting of at least:	
12. / / 2 13. / /		
14. 🗸	Erythrocyte count Hemoglobin Hematocrit Clinical chemistry at 6 month intervals consisting of at least; Alkaline phosphatase Total Protein Leucocyte count Platelet count (or clotting measure)	
	- Aspartate aminotransferase Albumin Creatinine kinase Urea Lactic dehydrogenase Inorganic phosphate	
·	Glucose Calcium Bilirubin Potassium Cholesterol Sodium Crestinine Chloride	
15	Urinalysis at 6 month intervals consisting of at least; Blood Total bilirubin Protein Urobilirubin Ketone bodies Sediment	
16	Appearance Specific gravity (osmolality) Glucose Volume Individual necropsy of all animals.	
17. 📆	Histopathology of the following tissues performed on all nonrodents and rodents, all control and high dose animals, all animals that died or were killed on study, all gross lesions on all animals, target organs on all animals and lungs, liver and kidneys on all other animals.	

Criteria marked with a * are supplemental and may not be required for every study.

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‡ The position document entitled "Selection of a Maximum Tolerated Dose (MTD) in Oncogenicity Studies (EPA No. 540/09-88-003) stated EPA's criteria for determining if an oncongenicity study has been adequately performed in terms of doses tested. However OPP is also aware that older oncogenicity studies, upon initial review or re-review. may have been tested at doses lower than the predicted MTD. In the event that such testing appears to be at doses less than the predicted MTD, the Office of Pesticides Program has been reviewing and considering the entire weight of the evidence to determine if retesting is necessary. Certain factors which affect the agency's decision to retest include but are not limited to the following: demonstrated oncogenicity in another species, nearness to the apparent MTD, genotoxic effects, structure-activity factors, absolute value of the highest dose tested and metabolic considerations.

[†] organs to be weighed.

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84-2 Mutagenicity Studies

MRIDA COI	H4969 (Ame. V) ACCEPTANCE CRITERIA (cylogenelic +) -maio* NA/Acc#071451/JERishry #412212 ady seet the following acceptance criteria?:
Does your st	ndy meet the following acceptance criteria?:
2	uirements echnical form of the active ingredient tested. legative, solvent and/or vehicle control(s) for the test system. ositive control(s) for the test system. uilly identified test system, species, strain, source etc. uilly described method for maintaining test system. uilly described method for preparing test environment and administering test compond. uilly described metabolic activation system, if required. etermination of maximum and range of concentrations/doses used under test conditions. riteria for determination of a positive effect.
1.	Requirements almonella reverse mutation assay linimum of four strains, TA98, TA100, TA1535 and TA1536. (alternatives need rationale) train specific positive controls. ighest concentration limited by toxicity, solubility or 5000 ug/plate. It least 5 different concentrations of test material at adequate intervals. single positive response confirmed by testing over a narrow range of concentrations. It least three plates experimental point. The enemutation in somatic cells in culture ighest concentration limited by toxicity (10-20% relative survival), solubility or 5000 ug/ml. It least 4 different concentrations of test material to yield a concentration related toxic fect.
3 Do	etermination of the number of cell cultures used. vitro mammalian cytogenetics ighest concentration limited by toxicity (e.g. reduced mitotic activity; alteration of cell cycle;
2. M 3. A 4. D	ultiple concentrations used to define the response. I least two independent cultures for each experimental point. etermination of culture harvest time.
1	vivo mammalian crioscenetics - bone marrow t least 5 male and 5 female animals per experimental group. ighest dose limited by toxicity or 5000 mg/kg. etermination of sampling times.
A	spaced with central sample at 24 hour (may be altered based on cell cycle time). b) repeated treatments - samples taken 6 and 24 hours after last treatment (may be

Criteria marked with a * are supplemental and may not be required for every study.

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altered based on cell cycle time).

Micronucleus; Samples taken 3 times, starting not earlier than 12 hours after the last treatment and at appropriate intervals following the first sample, but not beyond 72 hours.

Micronucleus assay, at least 1000 polychromatic erythrocytes/animal scored. Ratio of poly to normochromatic determined by counting 200-1000 erythrocytes (1000 OECD).

Rodent dominant lethal assay

1. _____ Sufficient number of dosed males to provide a minimum of 30 pregnant females per mating interval.

2. _____ Concurrent positive control or results from positive control conducted within 12 months in same laboratory with same strain.

3. ____ Highest dose produced toxicity or 5000 mg/kg.

Sampling or exposure over entire spermatogenesis cycle of dosed males (8 weeks mice, 10 weeks rats)

Any mutagenicity test with suggestive or greater positive results/activity shall be submitted requrdless of missing essential items.

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85-1 Metabolism Studies

ACCEPTANCE CRITERIA

MR10#00129345

Does you	if study meet the following acco	sptance criteria?:
1. 7	Analytically pure grade of the	e active ingredient.
2 7	Isotopically labeled in the co	ore of the molecule and/or significant portions thereof.
3	Analytical procedures sufficie	ently specific and sensitive to identify the test substance.
4. 🔽	Young adult rats. Other man	nmalian species may be used for specific purposes.
5. NC	Five male and five female ra	ts for each dose, 4 if following OECD protocol.
6. <u>NO</u>	Two doses, the low to be wit signs but not severe effects of	-OR- ently specific and sensitive to identify the test substance. In malian species may be used for specific purposes. Its for each dose, 4 if following OECD protocol. Ithout effect and the high to produce toxic or pharmacological or mortality.
7.* <u>NO</u>	Dosing group A, single low of normal saline).	dose by intravenous route (not required if insoluble in water or
8. NO	Dosing group B, single low d	lose by oral route. ive daily low dose of the unlabeled test material by oral route
9.	Dosing group C, 14 consecut	rive daily low dose of the unlabeled test material by oral route
	followed by a single low dose	e of the labeled test material.
10. <u>/ 0</u>	Dosing group D, single high	
11. 📈	Collect individually all urine,	, feces and expired air for 7 days after labeled dose or until 90+ed (whichever occurs first). Expired air not required if a pilot
_	study shows no excretion in !	
12 100		D, quantity of label in the following tissues and organs;
	bone	liver
	brain	· Inne
	<u></u> ✓ fat	blood wuscle
	testes	muscle
	heart	spleen
	heart kidney	residual carcass
	tissues showing pethol	ogy in this or prior studies
For all do	sing groups:	
l3. <u>/</u>		feces and expired air (if detected in preliminary study) at
	appropriate intervals (e.g. 4,	8, 12 and 24 hours, 1.5, 2, 3, 4, 5, 6 and 7 days.
14. NO		and feces to detect metabolism and identify metabolites (pooled
	urine and feces by dosing gre	oup may be used).

NOTE The metabolism data requirement may be filled in part. For example performing the analysis on

Criteria marked with a * are supplemental and may not be required for every study.

a single dose group can satisfy the requirement for that dose.

SRRD/GCSB TRANSMITTAL SHEET FOR PART B's Pirimiphos-methy Pesticide: Transmitted to HED on 1/-38-89 Chem. Tox.#: 33/8 Sponsor: TCT Americas Chemical#/Case#: 2535 CRM: Ruby Why Ler 5 This action contains a request for a DATA WAIVER ()/ TIME EXTENSION (). Label attached: Yes ()/ No (**) Reviewer: William B. Green Branch: Toxicology _____, Section _____ Completed: __/_/_ Concurrence: Response, by Guideline Guideline #: 81-1 Compliance Codes: Y/1 Description: Acute oral/rat Data Waiver ()/ Time Extension () MRID 00080716 study # 00030726 mit in tilliograph MRID # 00,2625-Discussion: inducted on a 75.4% form lating. Tox. cites 34.2.70. = co A study conducted on the technical Recommendation: Guideline #: 81-2 Description: Acute Dermal/rat Compliance Codes: Y/1 Data Waiver () / Time Extension () MRID 0008072-7 study # NA MRID# 00080727 met in Discussion: conclusted on a 75.4 90 formulation. How caticon III MRID # 00 1644 23 conducted on a 40 70 formulation. Technical in 94.290 conducted on the tophrud is resurre Recommendation : A slud or restain

ニア・ ア 名って こ た

Guideline #: <u>81</u>	<u>-3</u> Description: <u>Acute Inhalation/rat</u>
Compliance Code	s: // Data Waiver ()/ Time Extension ()
MRID <u>00126258</u>	, Study # C7L/P/602
Discussion:	MRID * 0 912 6258 was not conducted on technical.
	Conducted on a 75.4% formulation Tox coleran next
-	established. Nomina consentation reported. Teterminal
	≥94,290,
Recommendation	: A study conducted on the technical is required
	100 00:70/4)
	\$61780000
•	
Guideline #: <u>81</u>	
Compliance Code	es: // Data Waiver ()/ Time Extension ()
MRID OOKG4524	, Study # <u>CTL/P/1305</u>
Discussion:	MRID# Oct 64524 conducted on a 40% formulation, MRID#
	Oci26257 conducted on a 75.4% borne lation. Tox cateron
	II las 75,470 formulation, MRID#00080729 not in
	Tilliography, Technical so 94,270.
•	
Recommendation	: A studiconducted on the technical is required
Vecoume!!dacto!!	The same of the sa
	per / UNTERD .
•	
	•
	·
Guideline #: <u>81</u>	<u>-5</u> , Description: <u>Primary dermal irritation/rabbit</u>
Compliance Code	es: Y/ Data Waiver ()/ Time Extension ()
MRID <u>00080728</u>	, Study # <u>~~</u>
Discussion:	m R10 = 00080728 not in brillionagher MRIN = 00 126257
•	conducted on a 75.4% formulation, Tox. catecan TV.
	MRID+00164524 conducted on a 4070 formulation.
	Technical is 94,2%
	11111
•	
Recommend ation	· A study on lated in 40 at all in a
vecommender fou	By man conducted on the restrict in Algure
	- for review.
•	

	Guideline #: 81 Compliance Code MRID <u>CO129341</u> Discussion:	
•	Recommendation	The study MRID#00129341 is acceptable for
·		
	Guideline #: 81 Compliance Code MRID <u>00080711</u> Discussion:	
	Recommendation	: A study is not needed because the 90-day
·		
	Guideline #: 82 Compliance Code MRID <u>00080730</u> Discussion:	es: Y/l Data Waiver ()/ Time Extension ()
•	Recommendation	: The slind is not readed for neview
·		
		4
· ·		·

	Guideline #: 82 Compliance Code	s: Y/l Data Waiver ()/ Time Extension ()
	MRID <u>Socro742</u> Discussion:	MRID#S 00080742 and 00080743 notin Indianaphy.
		A 90-day day study is lested in the onl-littere.
	•	(Core-minimum) The DER was grammed but found be bottom brief to determine the adiquee of the stade Honore 2-4- chronic stud
		superiodes No regiment for the study.
	Recommendation	: The study is not readed for review.
v.	1/60011111011011	
	Guideline #: 82	
	Compliance Code	
	Discussion:	DER of MRID+00 129342 has been bramined and
		agreed to be adoqueted Core-Minimum)
	Recommendation	
		review.
	•	
	Guideline #: 82	2-3 Description: 90-day dermal/rodent
	Compliance Code	es: N/7 Data Waiver ()/ Time Extension ()
	MRID $N \rho$ Discussion:	The study is not various, under current use
	DISCUSSION.	potterns. I Code 7 indicatos "criteria not mot"
	.	: A study is not needed.
	Recommendation	: 11 study to not metalla
	, ·	
•		
		5
	•	
	•	

Compliance Code MRID NA	s: $N/7$ Data Waiver ()/ Time Extension () Study # NA
Discussion:	A study is not required under current use polleins. Code 7 tralectes "criteria met met"
Recommendation	: A study is not needed.
Guideline #: <u>82</u> Compliance Code MRID <u>のいなりよい</u> Discussion:	s: Y / Data Waiver () / Time Extension ()
Recommendation	The study MRID# 00126254 is acceptable for neview.
	-5(b) Description: 90-day neurotoxicity/ mammalian
Compliance Code MRID <u>NA</u> Discussion:	Code 7 indicates "criteries not met"
Recommendation	: Study is not needed at this time.

Guideline Compli-MRT-

Star		
	Guideline #: 83 Compliance Code MRID 00081912	s: Y/ Data Waiver ()/ Time Extension ()
	Discussion:	Of 10 # 00081312 was not in the bibliograph Newever a 2-40 Chanie/Orcopnic study is listed to the one-links. The DER has been bramened (block # HO/IH/P/113; 4/74) but was not brief to determine the address of the study.
	Recommendation	: The study should be submitted for review after being reformatted.
	Guideline #: <u>83</u> Compliance Code MRID <u>000807</u> 4억 Discussion:	
	Recommendation	5/5/73 is listed in the one-linery DER of study was branched but two brief to determine the adequay of the study (Cone-guidelihe) The study should be submitted for review after being reportabled.
	Guideline #: 83 Compliance Code MRID <u>Ooc81912</u> Discussion:	s: \frac{\frac{1}{2}}{2} Data Waiver ()/ Time Extension ()
	Recommendation	: Same as P3-1(a)

Guideline #: 83	-2(b) Description: Oncogenicity/mouse
Compliance Code	
MRID 00080740	
Discussion:	MRIO # 000 80746 was not in the biblionashy, 18th Am
	18-Mo Many shall # ICI 3417658: 7/15/78) to lister
	in the one-liver tile DER was examined but is
-	too will to determine the adequal of the study
	(Core-minimum)
Recommendation	: The short should be submitted for review
1,000	aller being reformatted
	the state of the s
Guideline #: 83	
Compliance Code	
MRID <u>00151623</u>	
Discussion:	DER of MRID# 00151623 has been excerned and
•	arrears to be acceptable. (Cone-surfaline)
· ·	
	1 h a a
Recommendation	: The study MRID#00151623 is acceptable for
	review ()
•	
Total Control of the	
Guideline #: 83	-3(a) Description: Teratogenicity/rat
Compliance Code	
MRID	
	, Study #
Discussion:	
Recommendation	
•	
4	

Guideline #: 83 Compliance Code	s: Y/ Data Waiver ()/ Time Extension ()
MRID <u>oco8073</u> Discussion: Start	MAID # 000 50734 pot in Irbliography, However a rabbit aturb is letter on the one-lines (btind#HC/CTL/P/II) Cone-Minimum DER after study has been champed but is too Irrief le delanne it de adequacy of the study
Recommendation	: The stud MRID #000 36734 should be reformatted and submitted of for neview.
Guideline #: 83 Compliance Code	B-3(c) Description: <u>Teratogenicity/mouse</u> es:한유/ 단위 Data Waiver ()/ Time Extension ()
MRID	
Discussion:	N/I
Recommendation	· NA
·	
•	· · · · · · · · · · · · · · · · · · ·
Guideline #: <u>83</u>	3 1-4 Description: 2-generation reprod./rat
Compliance Code MRID <u>00080735</u>	es: Y/ Data Waiver ()/ Time Extension () , Study # 5457/72/853
Discussion:	MRID# 5 00080735 and 00080736 are not in the
	[#ICI 63/76534: 8/3/176) and is Core-miring. A second start
Ī	hory been grammed but contain too little detail to determine if &
	: Tho two sludies MRIPS 00080735 and 00080736
Recommendation	TABLE AND A CONTRACTOR OF A STATE
Recommendation	should be submitted for review after being referretted

Guideline #: <u>84</u>	
Compliance Code	s: Y/ Data Waiver ()/ Time Extension ()
MRID <u>00144969</u> Discussion:	DER of MRID CO144969 has been grammed and
DISCUSSION.	arelan de la acceptable (Acceptable)
_	-0 1 1 000 d
Recommendation	
•	_ review.
	·
	-2(b) Description: Struct. chrom. aberration
Compliance Code	
MRID <u>00126256</u>	, study #
Discussion:	MRID+5 00 126256 and 00080733 are not in the
•	is on one-letters: (NO Care-rade) DER was grammad
•	Ind was too been to determine the along at the aterior
	The second of the sure
Recommendation	: The sluck should be submitted for never ofte being
	reformation.
•	
Guideline #: <u>84</u>	-2(c) Description: Other genotoxic effects
Compliance Code	
MRID <u>UA</u>	, study #,
Discussion:	A new study will be submitted.
•	<u> </u>
Recommendation	: The new study will be acceptable for review.

	-1 Description: General metabolism/rat
Compliance Code	s: // Data Waiver () / Time Extension ()
MRID <u>00129345</u>	
Discussion:	DER of MRID # 00129345 has been branched of agreem the a low close repeated dose study. The simply law and high done policing of the study flavor red been conducted. ((one minimum)
Recommendation	dose stuly. Am additional study is required for a single later and high - dose - dosing regimens. Should be reformabled
•	
Guideline #: <u>85</u> Compliance Code MRID <u>ドウ</u> Discussion:	Description: Dermal penetration s: N/7 Data Waiver ()/ Time Extension () Study # NA Code 7 inductes "Cutare not not". Devere, it was one proposed leaves the domical for to could flee an example. Too decides often received on superior excession, that a dermal penetration study was received to pursued.
Recommendation	use for capet treatment to contact floor
Guideline #: <u>86</u> Compliance Code MRID <u>NA</u> Discussion:	
•	experient openie.
Recommend atio n	use for coupet treatment to control fless is furneed.



011665

Chemical:

Pirimiphos-methyl (ANSI)

PC Code:

108102

HED File Code

13000 Tox Reviews

Memo Date:

04/04/90

File ID:

00000000

Accession Number:

412-02-0007

HED Records Reference Center 05/22/2002